Elevated PBDE Levels in Pet Cats: Sentinels for Humans?

JANICE A. DYE,*,† MARTA VENIER,‡ LINGYAN ZHU,‡,∥ CYNTHIA R. WARD,§ RONALD A. HITES,‡ AND LINDA S. BIRNBAUM†

U.S. Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Experimental Toxicology Division, Research Triangle Park, North Carolina 27711, School of Public and Environmental Affairs, Indiana University, Bloomington, Indiana 47405, and College of Veterinary Medicine, University of Georgia, Athens, Georgia 30602

Co-incident with the introduction of polybrominated diphenyl ethers (PBDEs) into household materials nearly 30 years ago, feline hyperthyroidism (FH) has increased dramatically. Risk of developing FH is associated with indoor living and consumption of canned cat food. We hypothesized that increases in FH were, in part, related to increased PBDE exposure, with key routes of exposure being diet and ingestion of house dust. This study was designed to determine whether body burdens of PBDEs in hyperthyroid (HT) cats were greater than that of young or sick non-HT cats. Serum samples and clinical information were collected from 23 cats. Serum and dry and canned cat food were analyzed for PBDEs. A spectrum of BDE congeners was detected in all cats, with BDE-47, 99, 207, and 209 predominating. Mean ± standard error (and median) cumulative ΣPBDE serum concentrations of young, old non-HT, and HT cats were 4.3 ± 1.5 (3.5), 10.5 ± 3.5 (5.9), and 12.7 ± 3.9 (6.2) ng/mL, respectively. Due to high variability within each group, no association was detected between HT cats and ΣPBDE levels. Indicative of age- or disease-dependent changes in PBDE metabolism, BDE-47/99 ratios were inversely correlated with age, and 47/99 and 100/99 ratios in HT cats were significantly lower than those in the other cats. Overall, ΣPBDE levels in cats were 20- to 100-fold greater than median levels in U.S. adults. Our results support the hypothesis that cats are highly exposed to PBDEs; hence, pet cats may serve as sentinels to better assess human exposure and adverse health outcomes related to low-level but chronic PBDE exposure.

Introduction

Since the first veterinary case reports in 1979 (*1*, *2*), feline hyperthyroidism (FH) has become a leading cause of morbidity in pet cats. During the 1980s, U.S. veterinary schools increasingly identified this heretofore-rare disease syndrome (*3*−*6*), with the earliest detectable increases occurring in California and in the Great Lakes region (*3*). Primarily affecting older cats, the average age at initial diagnosis was 13−14 years, with less than 5% of cats being diagnosed younger than 8 years of age (*7*, *8*). Clinical signs of FH (weight loss, polyphagia, and tachycardia) were due to increased T_4 levels owing to development of thyroid adenomatous hyperplasia and autonomously hyperfunctional benign nodules (*3*). The spectrum of thyroid pathologic changes in cats closely resembled that of toxic nodular goiter (TNG) in humans (*8*). While the etiopathogenesis of FH or TNG remains unknown, veterinary epidemiologic studies suggest that increased risk of developing FH is associated with indoor living and consumption of canned cat food, in particular fish flavors (*3*, *9*−*12*). At present, FH is the most common endocrinopathy in cats (*8*), and except for humans, cats are the only mammalian species with a high incidence of hyperthyroidism (*13*).

Co-incident with emergence of this syndrome in cats was the introduction of brominated flame-retardants into household materials to reduce the risk of fire. The first reports describing environmental contamination with polybrominated diphenyl ethers (PBDEs), a widely used class of brominated flame-retardant, were also published in 1979 (*14*, *15*). By the early 1980s, PBDE environmental levels had increased exponentially, most notably in the Great Lakes region (*16*, *17*) and California, with commensurate increases in fish, waterfowl, and marine mammals (*18*). Although increases in FH were first observed in the United States, this syndrome has since been recognized in Canada, Australia, New Zealand, Japan, and many parts of Europe (*7*, *9*). This distribution parallels that of countries that have since reported increased PBDE levels in the environment and wildlife (e.g., Canada, Australia, New Zealand, Japan, the UK, Sweden, Germany, and Belgium) (*17*, *19*−*21*). Importantly, PBDE levels are also increasing in people, with individuals in the United States having the highest levels reported worldwide (*17*, *22*). Owing to structural similarities of various BDE congeners (e.g., tetra-brominated BDE-47) with thyroxine (T_4), as well as reports on PBDE toxicological effects in laboratory rodents (*23*) and wildlife (*21*), there is growing concern over potential endocrine dysregulation in exposed humans (*24*).

We hypothesized that the increases in FH observed worldwide during the 1980s to present were, in part, linked to parallel increases in the use of brominated flame-retardants. We further hypothesized that PBDE exposure of pet cats—similar to that of their owners—would likely occur through diet (*25*, *26*) and contact with PBDE-containing household materials and dust (*19*, *27*). We suggest, therefore, that pet cats could serve as sentinels to better assess adverse human health outcomes related to low-level but chronic exposure to brominated flame-retardants. Hence, in this pilot investigation, we measured PBDE levels in 23 cat serum samples. The animals were divided into 3 groups: hyperthyroid cats, young cats (defined as ≤5 yrs), and older cats (≥8 yrs) with non-thyroidal illness. To evaluate dietary PBDE exposure in cats, the PBDE content of representative dry and canned cat food samples was also determined.

Experimental Section

Experimental details are given in the Supporting Information, and are briefly summarized here. Serum (1−2 mL) was obtained during 2005−2006 from client-owned cats in association with veterinary teaching hospitals in Georgia, Massachusetts, and North Carolina. Commercially available dry and pop-top cans of cat food products were purchased in Bloomington, Indiana, during 2005−2006. The serum

* Corresponding author e-mail: dye.janice@epa.gov.
† U.S. Environmental Protection Agency.
‡ Indiana University.
§ University of Georgia.
∥ Current address: College of Environmental Science and Engineering, Nankai University, 30071 Tianjin, People's Republic of China.

10.1021/es0708159 CCC: $37.00
Published on Web 00/00/0000

TABLE 1. Group Clinical Information and ΣPBDE Serum Concentrations in Cats Based on Health Status

indices	young	non-HT	hyperthyroid
group size	$n = 5$	$n = 7$	$n = 11$
sex ratio (M/F)	4:1	4:3	7:4
serum ΣPBDE (ng/mL)			
mean ± SE	4.3 ± 1.5	10.5 ± 3.5	12.7 ± 3.9
median	3.5	5.9	6.2
minimum/maximum	1.85−10.3	2.23 − 27.2	3.0 − 39.5
age (years)			
mean ± std err	2.55 ± 0.7	10.4 ± 1.1	14.2 ± 0.7
median	2.0	9.5	14.0
minimum/maximum	1.25 − 5	8−15	10−18
body condition score (BCS)			
mean (of 9 maximum)	4.5	4.9	4.7
minimum/maximum	3.5 − 5	2−9	1.5−7
recent change in weight			
mild gain		1/7 (15%)	1/11 (9%)
none	4/5 (80%)	1/7 (15%)	2/11 (18%)
mild loss		2/7 (28%)	3/11 (27%)
moderate loss		2/7 (28%)	4/11 (36%)
severe loss		1/7 (15%)	1/11 (9%)
NA[a]	1/5 (20%)		
diet type			
canned (mostly)	1/5 (20%)	0/7 (0%)	3/11 (30%)
mixed (dry + canned)	2/5 (40%)	3/7 (40%)	6/11 (50%)
dry (mostly)	2/5 (40%)	4/7 (60%)	2/11 (20%)
housing			
indoors only	3/5 (60%)	4/7 (56%)	8/11 (73%)
in and out	1/5 (20%)	1/7 (15%)	2/11 (18%)
NA[a]	1/5 (20%)	2/7 (28%)	1/11 (9%)

[a] NA: not available.

samples were denaturized with HCl and 2-propanol and extracted with hexane/methyl *t*-butyl ether. The food samples were Soxhlet extracted using hexane/acetone. All samples were analyzed by electron capture negative ionization gas chromatographic mass spectrometry for the major PBDE congeners. Data were analyzed using a *t*-test for single comparisons or an analysis of variance with Fisher's protected least-significance difference testing for determination of multiple group comparisons.

Results and Discussion

Subjects. Of the 23 cats evaluated, 12 had no evidence of FH including 5 young cats presenting for routine examination or acute conditions only (e.g., urethral blockage) and seven older cats presenting for a variety of non-thyroid-related conditions (e.g., diabetes, neoplasia, chronic dental, lung, intestinal, or renal disease). Of the 11 HT cats, the time from initial diagnosis of FH to serum procurement was 1 month to 3 years. Grouped by health status, clinical information [(i.e., age, diet, body condition scores (BCS)] is presented in Table 1. Due to difficulty in finding comparably aged cats that were not HT, the mean age of the sick non-HT cats was somewhat less than that of the HT cats. Importantly, the degree of recent weight loss and the mean (and range) of BCS in non-HT and HT cats were comparable.

PBDE Serum Concentrations: Influence of Age, Weight Loss, and Disease. A spectrum of PBDE congeners was detected in all cats. However, we were unable to accurately determine the corresponding lipid content of each sample due to the small sample volume; thus, results are expressed as the concentration of PBDEs in serum (i.e., ng PBDEs/mL). A stacked bar graph of the individual congeners comprising the group mean PBDE serum concentrations is depicted in Figure 1. The most consistently detected congeners were BDE-47, 99, 100, 153 154, 183, 207, 208, and 209; with other miscellaneous congeners (i.e., Σother BDE-66, 85, 196, 197, and 201) present in some cats but in much lesser quantities. Serum levels of all the other measured congeners were negligible.

Data indicated that HT cats had increased accumulation of "other" PBDEs (Σother PBDEs, mainly BDE-197 and 201) compared to young cats (Figure 1). Additionally, there was a trend toward increased BDE-183 in HT cats (0.31 ± 0.10 ng/mL) relative to young cats (0.059 ± 0.005 ng/mL) ($p = 0.06$). Although BDE-183 was not a prominent congener, its detection is consistent with exposure to the so-called "octa" commercial mixture (*28*). However, the "octa" mixture constituted only ~ 4% of the North American commercial PBDE market, and its production ceased as of 2004 (*24*).

Overall, the mean (±standard error) ΣPBDE serum concentrations in young, non-HT, and HT cats were 4.3 (±1.6), 10.5 (±3.5), and 12.7 (±3.9) ng/mL, respectively (Figure 1; Table 1). By comparison, the mean serum concentrations of BB-153 (from the long-banned Firemaster brominated biphenyl) were nearly 100-fold less [i.e., 0.047 (±0.034), 0.056 (±0.031), and 0.10 (± 0.07) ng/mL in young, non-HT, and HT cats, respectively]. Young cats had some of the lowest ΣPBDE levels detected; the highest levels occurred in HT cats with moderate weight loss. Within each subgroup, however, there were "outlier" cats, defined herein as having ΣPBDE serum levels 4−7-fold higher than other cats in their subgroup (Figure 2). Owing to this within-group variability, the mean ΣPBDE serum concentrations in young, non-HT, and HT cats were not significantly different ($p = 0.34$). In like manner to these cats, in the United States, certain adult humans also have blood levels that are 7−8 times higher than median PBDE levels (*22*). We further assessed whether aging significantly influenced ΣPBDE serum levels. When outlier cats were analyzed separately from non-outliers, simple linear regression of age and ΣPBDE concentrations revealed weak but positive correlations; with outlier cats accumulating relatively greater PBDE body burdens over time (Figure 2). In examining the cats as a whole, the high ΣPBDE levels in outlier cats could not be explained simply by disproportionate weight loss or excessively low BCS. For example, although the three-outlier HT cats all had moderate weight loss, the outlier young and non-HT cats had only mild to no weight loss. Moreover, based on BCS at the time of sampling, several of the non-outlier sick non-HT and HT cats were more emaciated than any of the so-called outlier cats (data on individual cats in Table S1 in the Supporting Information). Thus, generic factors such as aging and recent weight loss had only modest influences on overall PBDE serum concentrations, and no association was detected between HT cats and overall ΣPBDE serum levels.

The ratios of certain congeners were different in HT cats: data revealed that BDE-47/99 was significantly lower in HT cats (0.58 ± 0.12) compared to young (1.07 ± 0.15) and sick non-HT cats (1.04 ± 0.15) ($p \leq 0.03$). Similarly, HT cats had significantly reduced BDE-100/99 ratios (0.052 ± 0.008) relative to young (0.12 ± 0.02) and non-HT cats (0.10 ± 0.02) ($p \leq 0.004$). Overall, there was a significant but inverse correlation between age and BDE-47/99 ratios ($R = 0.71$; $p = 0.0001$). These findings suggest that, while BDE-99 was a predominant congener in most cats, this congener was particularly abundant in many of the older HT cats. With one exception, the average BDE-47/99 ratio in HT cats was ~1:2. The exception, a 14-yr-old cat noted to eat canned salmon, had a BDE-47/99 ratio ~2:1. The observation that older cats have significantly decreased BDE-47/99 and BDE-100/99 ratios suggests the possibility that, with advancing age, cats may have reductions in their ability to metabolize certain PBDE congeners.

Comparison to PBDEs in Cat Food. To explain the high cat-to-cat variability observed, all cats were regrouped based on eating habits: (a) predominantly dry food; (b) mixed (dry + canned) food; and (c) predominantly canned food. Data

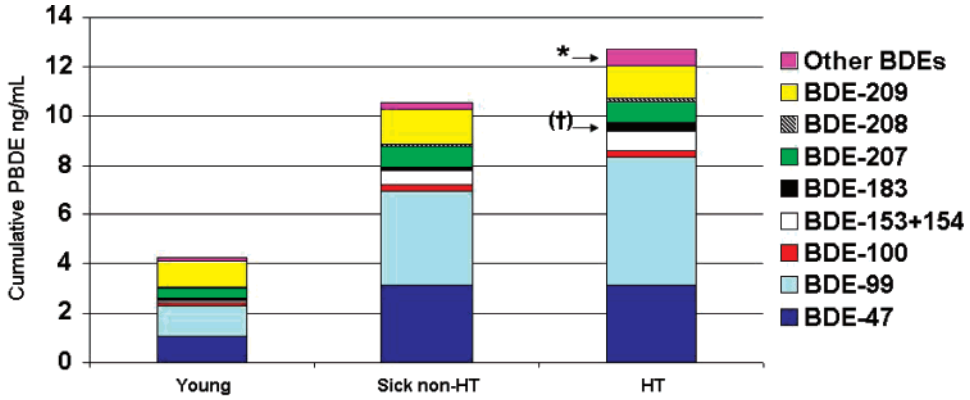

FIGURE 1. Mean ΣPBDE serum concentrations of the major tetra- to deca-brominated congeners in cats, stratified by health status (ng/mL). (*) Indicates significantly different from young cats ($p = 0.04$). (†) Indicates trend only in significant difference from young cats ($p = 0.06$).

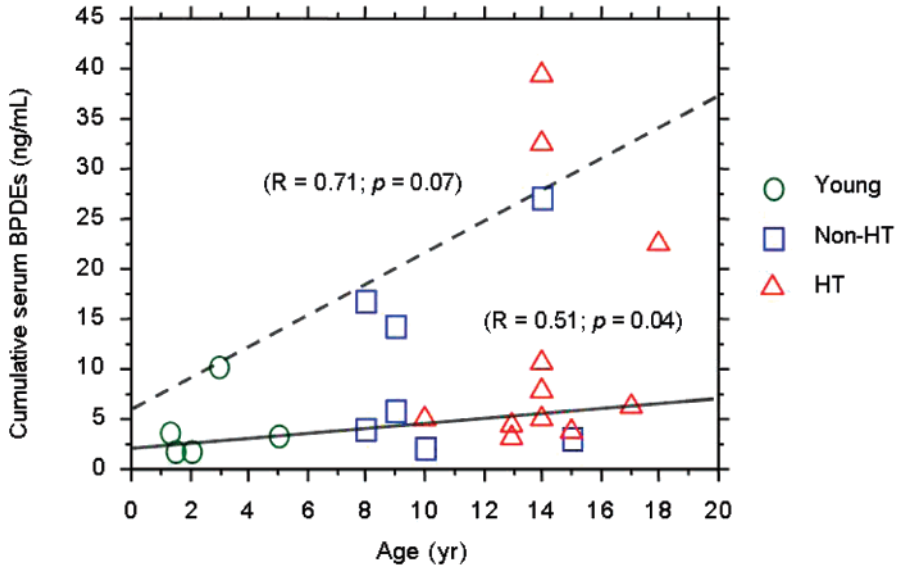

FIGURE 2. Correlation of ΣPBDE serum concentrations (ng/mL) with age (yrs) in outlier (- - -) and non-outlier (—) cats.

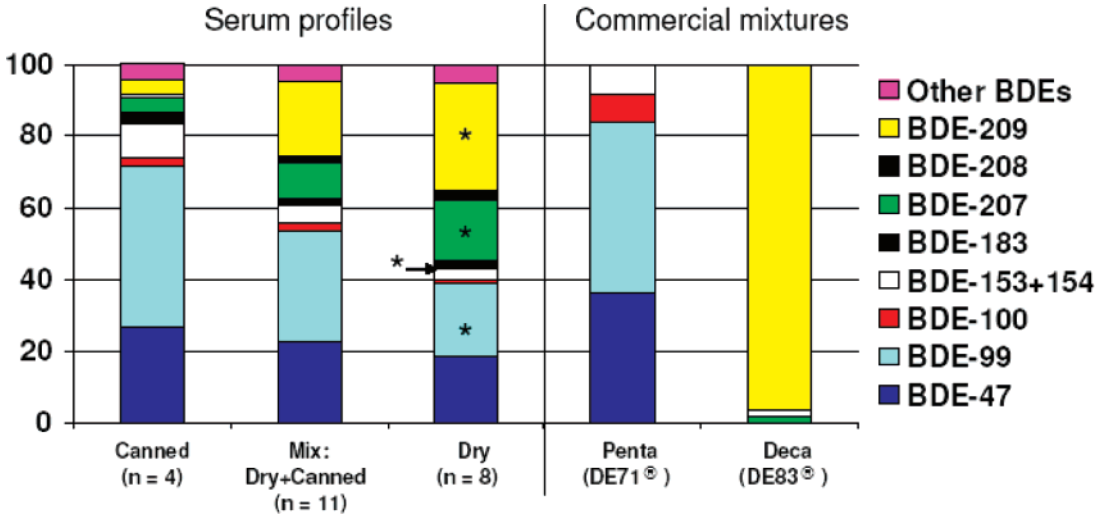

FIGURE 3. Mean serum PBDE congener profiles in cats (% of the ΣPBDE concentrations) stratified by diet type. Comparison to penta and deca commercial mixtures. (*) Indicates significantly different from cats eating canned food.

indicated that in canned-food eaters ($n = 4$), relatively little BDE-207 or 209 was present, thus allowing BDE-47 and 99 to predominate. Conversely, in dry-food eaters ($n = 8$), BDE-209 > 207 ≈ 47 ≈ 99 (Figure 3). As a group, cats eating a mixture of dry plus canned food ($n = 11$) exhibited a composite of these patterns (Figure 3).

We questioned why cats eating canned food had proportionately greater body burdens of BDE-47 and 99 (or alternatively, why they had less BDE-209). Detection of BDE-47 and 99 is consistent with exposure to "penta" commercial mixtures (e.g., DE-71) (Figure 3), which was almost exclusively used in North America (*29*). Despite being phased out in

TABLE 2. Comparison of the ΣPBDE Concentrations (mean ± SE) in Canned and Dry Cat Food (ng/g Wet Weight), Mean Concentrations of Select Congeners (ng/g Wet Weight), and % Lipid Content

	ΣPBDE (ng/g wet wt)	BDE- 47 (ng/g wet wt)	BDE- 99 (ng/g wet wt)	BDE-100 (ng/g wet wt)	BDE-153+154 (ng/g wet wt)	BDE-183 (ng/g wet wt)	BDE-207 (ng/g wet wt)	BDE-209 (ng/g wet wt)	% lipid	*N*
Canned food										
turkey-combo[a]	0.36 ± 0.19	0.06	0.04	0.02	0.03	0.07	0.06	0.02	9	3
chicken[a]	0.31 ± 0.06	0.13	0.04	0.03	0.02	0.02	0.006	0.009	4	3
chicken-combo[a]	0.17 ± 0.07	0.06	0.04	0.014	0.009	0.003	0.003	0.025	6	4
beef	0.36 ± 0.04	0.16	0.05	0.03	0.02	0.04	0.01	0.003	8	2
tuna	0.58 ± 0.09	0.25	0.13	0.05	0.04	0.02	0	0.01	6	2
whitefish	1.00 ± 0.20	0.26	0.05	0.05	0.08	0.19	0.06	0.04	8	4
salmon[a]	1.25 ± 0.03	0.80	0.08	0.15	0.04	0.01	0.002	0.008	8	4
seafood buffet	1.75 ± 0.02	1.09	0.20	0.20	0.06	0.007	0.003	0.016	4	2
Dry food										
chicken	0.6 ± 0.1	0.05	0.03	0.01	0.007	0.01	0.01	0.42	10	2
salmon	1.5 ± 0.1	0.06	0.03	0.01	0.005	0.03	0.04	1.04	10	2
poultry and fish	2.1 ± 0.4	0.04	0.04	0.01	0.009	0.009	0.03	1.89	8	4
adult	2.9 ± 0.1	0.06	0.08	0.02	0	0.06	0.07	2.28	21	4

[a] The value presented is the average between similar flavors of two different brands.

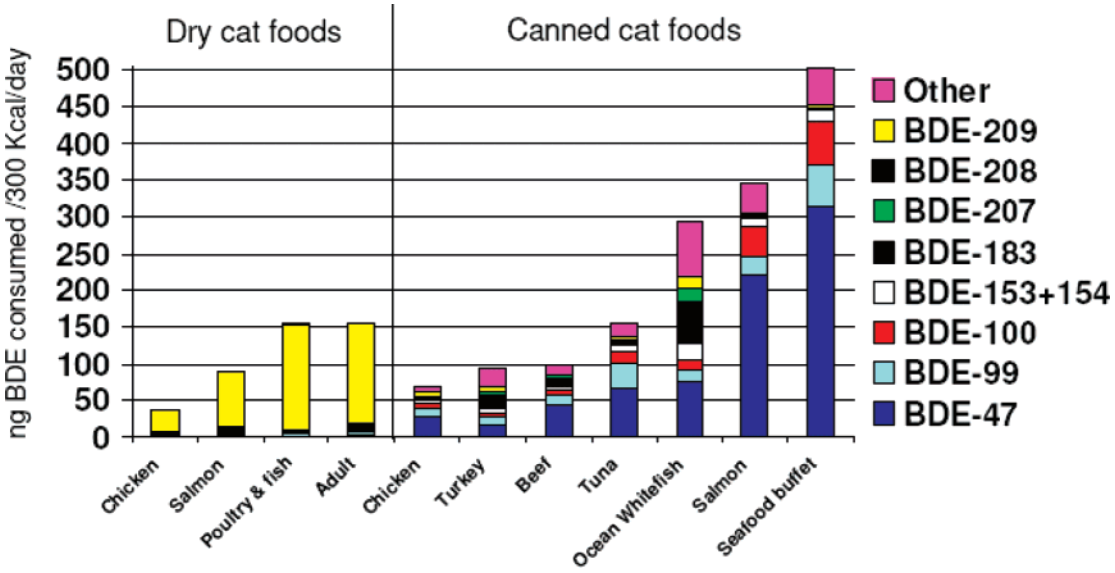

FIGURE 4. Estimated daily PBDE consumption in cats (ng BDE/300 Kcal/day) for a variety of dry and canned cat foods.

2004, it had been routinely incorporated into polyurethane foam and components of carpet padding, furniture, and mattresses, products likely to remain in homes for many years (*24*). In contrast, cats eating dry food had increased BDE-209 levels. "Deca" commercial mixtures (e.g., DE-83) were, and still are used in high-impact polystyrene, commercial textiles (upholstery), and electronic equipment (*28*) (Figure 3). By the late 1990s, deca's use was nearly 25,000 metric tons/year in North America alone, constituting nearly half the global demand for PBDEs (*29*).

To understand how diet influenced the cats' congener profiles, PBDE compositions of representative dry and canned cat foods were determined. Total ΣPBDE levels, on a wet weight basis, along with the lipid content of the food products are presented in Table 2. Overall, PBDE content of canned fish/seafood flavors was higher than non-seafood canned varieties. Data are consistent with recent reports on PBDE levels in edible marine species (*30*) and corresponding human food products (*25*, *26*). Assuming that these cat foods represented complete and balanced diets, and that a 4−5 kg cat requires 300 Kcal/day, the PBDEs contained in daily food consumed on these diets were calculated (Figure 4). It is apparent that cats consuming fish- or seafood "flavored" canned foods would ingest significantly more PBDEs (up to 500 ng PBDEs/day) compared to cats eating dry food or other canned varieties. Compatible with BDE-47 biomagnification in fish, the increased PBDE content of canned foods largely reflected increases in BDE-47. Mean BDE-47/99 ratios increased accordingly [i.e., dry food (1.5), canned poultry and beef (2.5), generic fish (4.3), and salmon (9.4)]. Among the 11 HT cats studied, there were two mixed food eaters whose dry food was supplemented with fish-based canned food. One cat reportedly ate one can of tuna-food/day, and it had a moderately high PBDE level of 10.6 ng/mL, and the second received dry food plus canned salmon, and it had an increased BDE-47/99 ratio of nearly 2:1.

Unexpectedly, dry food contained relatively high levels of BDE-209 (83−93% of total) with minor quantities of BDE-206 (4−7%) and 207 (1−3%), thus closely matching the commercial "deca" profile (*29*). We speculate that the BDE-209 content of dry food did not relate to base protein/fat sources as much as to processing. Detection of BDE-209 in dry food largely explained its prominence in dry-food-eating cats; with BDE-209 accounting for 4.2%, 21%, and 30% of serum ΣPBDE levels in canned-, mixed-, and dry-food-eaters, respectively. However, BDE-207 comprised only 1−3% of

dry food PBDE content and yet serum levels were nearly 50% that of BDE-209. Specifically, BDE-207 accounted for 4.5%, 9.8%, and 17% of the ΣPBDE levels detected in canned-, mixed-, and dry-food-eaters, respectively. The ratio of BDE-207/209 in dry food was only ~0.03; in serum, ratios were greater and remarkably constant [0.51 (±0.14), 0.54 (±0.11), and 0.63 (± 0.11) in young, non-HT, and HT cats, respectively]. These data suggest that in cats, BDE-207 is a major (meta-position) debromination product of BDE-209, differences in elimination half-lives between BDE-207 and 209 notwithstanding (*31*). The relative levels of highly brominated congeners (i.e., BDE-206 to 209) observed in cats are compatible with recent reports in humans (*31*), cows (*32*), rats (*33*), and birds (*34*).

Comparison to PBDEs in House Dust. Of the four most prominent congeners detected in cats (i.e., BDE-47, 99, 207, and 209), increased BDE-209 was seemingly associated with dry food consumption, and BDE-207 likely represented a debromination product. Although increased BDE-47 could relate to consumption of fish-based canned food, none of the cats consumed these flavors exclusively. Therefore, because house dust contains relatively high PBDE levels (*19*, *28*), we hypothesized that serum levels of BDE-47 and 99 in cats, in particular in the outlier cats, were most likely due to indoor exposure to PBDEs. While sleeping, cats would have direct and prolonged contact with upholstery, carpeting, and mattress materials. Due to their heat-seeking tendencies, cats frequently sit near (or even on) electronic equipment (e.g., computer monitors and television sets). Because of their meticulous grooming behavior, cats would effectively ingest any volatilized PBDEs or PBDE-laden dust that deposited on their fur during such activities.

Closer examination of outlier ($n = 7$) vs non-outlier ($n = 16$) cats revealed that mean ΣPBDE serum concentrations in outlier cats were 23.3 (±3.9) ng/mL, nearly 5-fold greater than in non-outlier cats at 4.5 (±0.58) ng/mL. The higher levels reflected significantly greater concentrations of BDE-47, 99, 100, 153+154 (i.e., congeners in the penta mixture), and BDE-183 (i.e., the main congener in the octa mixture) but not BDE-207 or 209. The relative proportion of BDE-47/99/100/153+154 in outlier and non-outlier cats (9:13:1:2 and 8:13:1:3, respectively) and commercial penta mixtures (e.g., DE-71 at 8:12:2:2) were similar. However, in outlier cats, penta-based congeners comprised ≥80% of the ΣPBDEs detected; while in non-outlier cats these congeners represented ≤50% of the ΣPBDEs detected (Figure S1).

As in cat serum, PBDE profiles for dust samples from homes in the eastern United States also revealed the presence of both penta- and deca-based congeners (*27*, *28*). Likewise, there was considerable dust-to-dust variability in the specific profiles detected. Analogous to our cats, ΣPBDE levels in dust from certain "outlier" houses were approximately 2.5- to 5-fold higher than dust from average households. Moreover, congener profiles of many such "outlier dust" samples (i.e., >6000 ng/g dry mass) reflected proportionately greater contamination with penta-based congeners (up to 90% of the ΣPBDEs detected). Taken together, these data are consistent with the hypothesis that increased indoor exposure to penta-laden house dust contributed to increased serum BDE-47 and 99 levels in cats, particularly the outlier subjects. Prospective studies in cats are needed to confirm this hypothesis. However, Wu et al. recently reported significant positive associations between PBDE levels in house dust and breast milk samples of the human occupants (*27*).

Comparison of Cats to Humans. Given that cats share the same household environment as their owners, it is interesting to compare their PBDE levels with those of humans. In U.S. adults, whole blood PBDE levels (including congeners BDE-47, 66, 85, 99, 100, 138, 153, 154, 183, and 209, but not BDE-207) are much lower (*22*). Median blood levels from men and women in the eastern United States ($n = 39$, collected in 2003) were, respectively, 0.10 and 0.19 ng ΣPBDE/mL. Also, as was observed in the cats, certain individuals had values 7−8 times higher than the median value for the corresponding sex, with the highest levels observed in men and women being 0.76 and 1.8 ng/mL, respectively. Thus, even our non-outlier young cats had serum ΣPBDE levels that were ~20 times greater than the median values reported for U.S. adults. Remarkably, the outlier HT cats had ΣPBDE levels that were more than 100 times greater.

In an effort to assess why pet cats have such high body burdens of PBDEs, we used this collective data set to estimate the relative contribution of dietary vs dust exposure in cats, as well as the relative exposure estimates in cats to that of humans in the United States. First, through dietary exposure we predict that dry-food-eating cats consume between 10 and 40 ng PBDE/kg/day; while canned-food eaters consume between 20 and 125 ng PBDE/kg/day. Estimates of daily PBDE consumption in adult humans range from a low of 21 ng/day in Spain (*30*), 31−44 ng/day in Sweden and Canada (*20*), to 88 ng/day in the United States (*26*). Assuming a typical adult weighs 70 kg, these data predict that on average, adult humans consume only 0.3−1.3 ng PBDE/kg/day. Hence, pet cats may be receiving 10−100 times greater dietary PBDE exposure than U.S. adults.

Next, based on (a) differences in serum BDE-207 + 209 levels between canned- vs dry-food eaters, (b) average ng of BDE-209 consumed by dry-food eaters/day, and (c) average house dust BDE-209 content (*28*), we estimate that cats consume ~5 mg dust/kg/day. According to U.S. EPA estimates for dust consumption in adults (50 mg dust/day) (*35*), a 70 kg adult would consume only 0.7 mg dust/kg/day. Thus, cats likely ingest 7-fold more dust than adult humans. In children, dust consumption is reportedly higher, accounting for up to 80% of total daily PBDE exposure (*19*), with estimates falling between 20 and 200 mg of dust/day (*28*). Assuming that a 2-year-old weighs 14 kg, young children are predicted to consume between 1.4 and 14 mg/kg/day, comparable to our estimate for cats. These predictions are also compatible with a recent case study wherein children, aged 18 months and 5 years, had higher PBDE serum levels (2.5 and 1.2 ng ΣPBDE/mL, respectively) than their parents (*36*). The ages and PBDE serum levels of these children were comparable to those of our non-outlier young cats. Hence, with regards to dust ingestion, cats (with their grooming behavior) may be suitable as sentinels for toddlers (with their increased floor contact time and "mouthing" behavior). With maturation, children would presumably ingest less dust, while cats would continue to engage in grooming, likely contributing to their persistently high PBDE body burdens.

To conclude, we predict that minimum PBDE exposure would occur in pet cats eating dry food and living in average deca-contaminated households. Such cats are estimated to consume ~65 ng BDE-209/kg/day (half through diet and half through dust ingestion). At the other extreme, maximal PBDE exposure would occur in canned-seafood-eating cats living in highly penta-contaminated houses. These cats are estimated to consume up to 250 ng of penta-based congeners (47 + 99 + 100 + 153 + 154)/kg/day (again approximately half via diet and half via dust).

Risk Factors for FH. Recognizing that FH appeared nationwide in the United States and then worldwide, all within a relatively narrow time interval, it seemed probable that some global change must underlie this condition. A number of theories arose as to specific factors that may have contributed to the transformation of a cat's normal thyroid into a nodular hyperfunctioning goiter. As recently reviewed (*7*), theories included immunological and nutritional changes as well as exposure to various environmental chemicals (*3*, *10*).

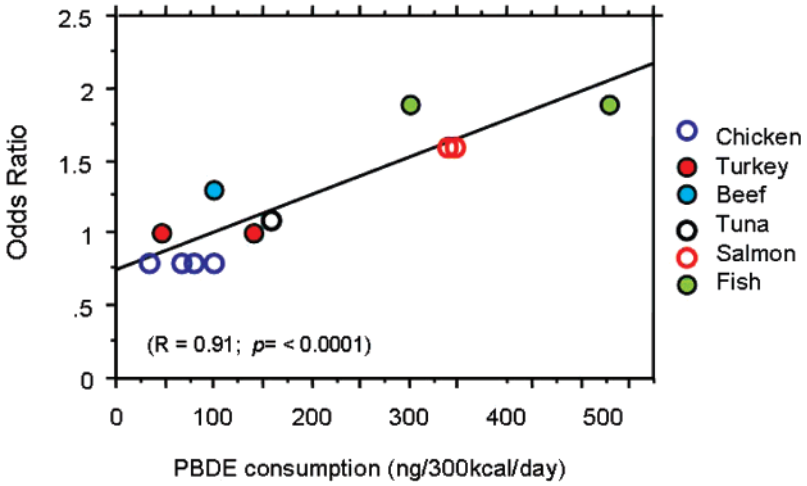

FIGURE 5. Correlation of calculated daily PBDE consumption (ng BDE/300 Kcal/day) for various canned cat food flavors analyzed herein vs overall odds ratio (OR) for developing feline hyperthyroidism as reported by Martin et al. (*12*).

To this list, we add exposure to yet another ubiquitous environmental contaminant, PBDEs. Circumstantial evidence indicates that the onset of and geographic distribution of PBDE usage rather closely paralleled the increases noted in FH. For instance, certain regions (such as the state of California) were more proactive in incorporating flame-retardant materials to decrease risk of fire. This may explain the disproportionate increase of HT cats at California's veterinary teaching hospital in the 1980s.

In comparing our data to risk factors previously identified for developing FH, dietary risk factors are in good accord with PBDE levels detected in cat food. For example, Scarlett et al. (*3*) reported a dose−response in risk for cats eating commercial canned cat food; with cats whose diet consisted of some but less than half canned food having 1.6 times increased risk, and cats fed more than half canned food having 3.4 times the risk. Regardless of life stage examined [kitten, young adult, and older adult (> 7 yr)], canned food consumption was associated with a greater risk of developing FH (*10*). Likewise, a New Zealand study concluded that increased risk was associated with eating a variety of canned flavors (odds ratio = 3.8) (*9*). [An odds ratio (OR) of 1 indicates that the condition under study is equally likely in the exposed and in the control groups; an odds ratio greater than 1 indicates that the condition is more likely in the exposed group; and an odds ratio less than 1 indicates that the condition is less likely in the exposed group.] A larger case-control study reported that cats eating 50−74% or 75−100% canned food had significantly increased risk (OR = 2.50 or 1.93, respectively) (*11*). Conversely, regular use of non-commercial dietary supplements, in particular beef or poultry, was associated with decreased risk (OR = 0.083 and OR = 0.43), respectively. Neither decreased nor increased risk was noted with dry food consumption. Finally, another case-control study reported that risk was increased in cats that preferred fish or liver and giblets flavors of canned cat food (*12*). No increase in risk was associated with chicken, poultry, turkey, beef, or tuna flavors. We observed a significant and robust correlation between the overall odds ratios as reported by Martin et al. (*12*) and the ng PBDE consumed/300 Kcal/day calculated herein for the corresponding "flavor" (Figure 5). Furthermore, limited data from a recent market survey indicated that, on a wet weight basis, the PBDE content in chicken liver was as high as that in salmon (*25*).

Nevertheless, one-quarter of HT cats reportedly never ate canned cat food (*10*), suggesting that additional risk factors are at play. To this end, Scarlett et al. (*3*) originally reported that increased risk was strongly associated with living predominantly (OR = 11.2) or strictly (OR = 4.0) indoors. Kass et al. (*11*) reported that increased risk was associated with use of cat litter, risk that again, could reflect indoor housing status. Recently, a New Zealand report found that cats sleeping predominantly on the floor were at increased risk (OR = 6.6) (*9*). Such cats would be in direct and prolonged contact with carpeting and dust accumulations. Thus, increased risk associated with indoor living is consistent with data on PBDE content in house dust (*27*, *28*).

Our results demonstrate that cats are being consistently exposed to PBDEs, an endocrine-disrupting environmental contaminant. By extension, due to prolonged PBDE exposure, cats may be at increased risk for developing thyroid compensatory hyperplastic changes (i.e., FH). Future studies will be necessary to determine to what extent increased PBDE body burdens of the magnitude detected herein may interfere with thyroid homeostasis in cats. If more definitive associations between PBDE exposure and altered T_4 levels can be established, then data from these "sentinel" cats suggest that chronic (cumulative) low-dose PBDE exposure may be more endocrine disrupting than would be predicted by most short-term (*37*) or even chronic PBDE exposure studies in laboratory rodents (*23*). Improved understanding of PBDE-related endocrine effects in cats may have public health ramifications for both veterinary and human patients alike.

Acknowledgments

We thank Drs. Margaret Edwards, Cary, NC; Marion Haber, Tonya Boyle, and colleagues at the College of Veterinary Medicine, North Carolina State University, Raleigh, NC; and Dr. Elizabeth Rozanski and colleagues at the Cummings School of Veterinary School, Tufts University, New Grafton, MA, for assistance on this study. We thank Drs. Karyn Harrell, Heather Stapleton, and Vicki Richardson for critical review of this manuscript. Drs. Dye and Venier share equally as primary authors, and Drs. Birnbaum and Hites share equally as senior authors. The information in this document has been subjected to review by the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Supporting Information Available

Additional clinical information on individual cats and further details on sample extraction and analysis, Figure S1, and Table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Peterson, M. E.; Johnson, G. F.; Andrews, L. K. Spontaneous hyperthyroidism in the cat. In *Proceedings of the American College of Veterinary Internal Medicine Forum*; 1979; p 108.

(2) Cotter, S. M. Uncommon disorders in the cat. In *Proceedings of the 45th Annual Meeting of the American Animal Hospital Association*; 1979; pp 115−117.

(3) Scarlett, J. M.; Moise, N. S.; Rayl, J. Feline hyperthyroidism: A descriptive and case-control study. *Prev. Vet. Med.* **1988**, *6*, 295−308.

(4) Holzworth, J.; Theran, P.; Carpenter, J. L.; Harpster, N. K.; Todoroff, R. J. Hyperthyroidism in the cat: ten cases. *J. Am. Vet. Med. Assoc.* **1980**, *176*, 345−53.

(5) Peterson, M. E.; Kintzer, P. P.; Cavangh, P. G.; Fox, P. R.; Ferguson, D. C.; Johnson, G. F.; Becker, D. V. Feline hyperthyroidism: pretreatment clinical and laboratory evaluation of 131 cases. *J. Am. Vet. Med. Assoc.* **1983**, *183*, 103−10.

(6) Thoday, K. L.; Mooney, C. T. Historical, clinical and laboratory features of 126 hyperthyroid cats. *Vet. Rec.* **1992**, *313*, 257−64.

(7) Gunn-Moore, D. Feline endocrinopathies. *Vet. Clin. Small Anim.* **2005**, *35*, 171−201.

(8) Gerber, H.; Peter, H.; Ferguson, D. C.; Peterson, M. E. Etiopathology of feline toxic nodular goiter. *Vet. Clin. North Am. Small Anim. Pract.* **1994**, *24*, 541−565.

(9) Olczak, J.; Jones, B. R.; Pfeiffer, D. U.; Squires, R. A.; Morris, R. S.; Markwell, P. J. Multivariate analysis of risk factors for feline hyperthyroidism in New Zealand. *N. Z. Vet. J.* **2005**, *523*, 53−58.

(10) Edinboro, C. H.; Scott-Moncrieff, J. C.; Janovitz, E.; Thacker, H. L.; Glickman, L. T. Epidemiologic study of relationships between consumption of commercial canned food and risk of hyperthyroidism in cats. *J. Am. Vet. Med. Assoc.* **2004**, *224*, 879−886.

(11) Kass, P. H.; Peterson, M. E.; Levy, J.; James, K.; Becker, D. V.; Cowgill, L. D. Evaluation of environmental, nutritional, and host factors in cats with hyperthyroidism. *J. Vet. Intern. Med.* **1999**, *13*, 323−329.

(12) Martin, K. M.; Rossing M. A.; Ryland, L. M.; DiGiacomo, R. F.; Freitag, W. A. Evaluation of dietary and environmental risk factors for hyperthyroidism in cats. *J. Am. Vet. Med. Assoc.* **2000**, *217*, 853−856.

(13) Nguyen, L. Q.; Arseven, O. K.; Gerber, H.; Stein, B. S.; Jameson, J. L.; Kopp, P. Cloning of the cat TSH receptor and evidence against an autoimmune etiology of feline hyperthyroid-ism. *Endocrinology* **2002**, *143*, 395−402.

(14) DeCarlo, V. J. Studies on brominated chemicals in the environment. *Ann. N.Y. Acad. Sci.* **1979**, *320*, 678−681.

(15) Zweidinger, R. A.; Cooper, S. D.; and Pellizzari, E. D. Identification and quantitation of brominated fire retardants. In *Measurement of Organic Pollutants in Water and Waste Water, ASTM STP 686*; Van Hall, C. E., Ed.; American Society for Testing and Materials: Philadelphia, PA, 1979; pp 234−250.

(16) Zhu, L. Y.; Hites, R. A. Temporal trends and spatial distributions of brominated flame retardants in archived fishes from the Great Lakes. *Environ. Sci. Technol.* **2004**, *38*, 2779−2784.

(17) Hites, R. A. Polybrominated diphenyl ethers in the environment and in people: A meta-analysis of concentrations. *Environ. Sci. Technol.* **2004**, *38*, 945−56.

(18) She, J.; Petreas, M.; Winkler, J.; Visita, P.; McKinney, M.; Kopec, D. PBDEs in the San Francisco Bay area: measurements in harbor seal blubber and human breast adipose tissue. *Chemosphere* **2002**, *46*, 697−707.

(19) Wilford, B. E.; Shoeib, M.; Harner, T.; Zhu, J.; Jones, KC. Brominated diphenyl ethers in indoor dust in Ottawa, Canada: Implication for sources and exposure. *Environ. Sci. Technol.* **2005**, *39*, 7027−7035.

(20) Ryan, J. K.; Patry, B. Body burdens and food exposure in Canada for polybrominated diphenyl ethers (BDEs). *Organohalogen Compd.* **2001**, *52*, 226−229.

(21) Darnerud, O. Toxic effects of brominated flame retardants in man and in wildlife. *Environ. Int.* **2003**, *29*, 841−853.

(22) Schecter, A.; Papke, O.; Tung, K. C.; Harris, J. J.; Dahlgren, J. Polybrominated diphenyl ether flame retardants in the U.S. population: current levels, temporal trends, and comparison with dioxins, dibenzofurans, and polychlorinated biphenyls. *J. Occup. Environ. Med.* **2005**, *47*, 199−211.

(23) National Toxicology Program (NTP). NTP Toxicology and Carcinogenesis Studies of Decabromodiphenyl Oxide (CAS No. 1163-19-5) in F344/N Rats and B6C3F1 Mice (Feed Studies). *Natl. Toxicol. Program Tech. Rep. Ser.* **1986**, *309*, 1−242.

(24) Birnbaum, L. S.; Staskal, D. F. Brominated flame retardants: cause for concern? *Environ. Health Perspect.* **2004**, *112*, 9−17.

(25) Schecter, A.; Papke, O.; Tung, K. C.; Staskal, D.; Birnbaum, L. Polybrominated diphenyl ethers contamination of United States food. *Environ. Sci. Technol.* **2004**, *38*, 5306−11.

(26) Schecter, A.; Papke, O.; Harris, R.; Tung, K. C.; Musumba, A.; Olson, J.; Birnbaum, L. Polybrominated diphenyl ether (PBDE) levels in an expanded market basket survey of U.S. food and estimated PBDE dietary intake by age and sex. *Environ. Health Perspect.* **2006**, *114*, 1515−1520.

(27) Wu, N.; Herrmann, T.; Paepke, O.; Tickner, J.; Hale, R.; Harvey, E.; La Guardia, M.; McClean, M. D.; Webster, T. F. Human exposure to PBDEs: Associations of PBDE body burdens with food consumption and house dust concentrations. *Environ. Sci. Technol.* **2007**, *41*, 1584−1589.

(28) Stapleton, H. M.; Dodder, N. G.; Offenbery, J. H.; Schantz, M. M.; Wise, S. A. Polybrominated diphenyl ethers in house dust and clothes dryer lint. *Environ. Sci. Technol.* **2005**, *39*, 925−31.

(29) Alaee, M.; Arias, P.; Sjodin, A.; Bergman, A. An overview of commercially used brominated flame-retardants, their applications, their use patterns in different countries/regions and possible modes of release. *Environ. Int.* **2003**, *29*, 683−689.

(30) Domingo, J. L.; Bocio, A.; Falco, G.; Llobet, J. M. Exposure to PBDEs and PCDEs associated with the consumption of edible marine species. *Environ. Sci. Technol.* **2006**, *40*, 4393−4399.

(31) Thuresson, K.; Hoglund, P.; Hagmar, L.; Sjodin, A.; Bergman, A.; Jakobsson, K. Apparent half-lives of hepta- to deca-brominated diphenyl ethers in human serum as determined in occupationally exposed workers. *Environ. Health Perspect.* **2006**, *114*, 176−181.

(32) Kierkegarrd, A.; Asplund, L.; De Wit, C. A.; McLachlan, M. S.; Thomas, G. O.; Sweetman, A. J.; Jones, K. C. Fate of higher brominated PBDEs in lactating cows. *Environ. Sci. Technol.* **2007**, *41*, 417−423.

(33) Huwe, J. K.; Smith, D. J. Accumulation, whole-body depletion, and debromination of decabromodiphenyl ether (BDE-209) in male Sprague-Dawley rats following dietary exposure. *Chemosphere* **2007**, *66*, 259−266.

(34) Van den Steen, E.; Covaci, A.; Jaspers, V. L. B.; Dauwe, T.; Voorspoels, S.; Eens, M.; Pinxten, R. Accumulation, tissue-specific distribution and debromination of decabromodiphenyl ether (BDE 209) in European starlings (*Sturnus vulgaris*). *Environ. Pollut.* **2006**, *148*, 648−653.

(35) U.S. EPA. *Exposure Factors Handbook, Vol. 1 − General Factors;* U.S. Government Printing Office: Washington DC, 1997; EPA/600P-95/002.

(36) Fisher, D.; Hooper, K.; Athanasiadou, M.; Athanassiadis, I.; Bergman, A. Children show highest levels of polybrominated diphenyl ethers in a California family of four: A case study. *Environ. Health Perspect.* **2006**, *114*, 1581−1584.

(37) Darnerud, P. O.; Aune, M.; Larsson, L.; Hallgren, S. Plasma PBDE and thyroxine levels in rats exposed to Bromkal or BDE-47. *Chemosphere* **2007**, *67*, S386−392.

Received for review April 6, 2007. Revised manuscript received July 10, 2007. Accepted July 10, 2007.

ES0708159